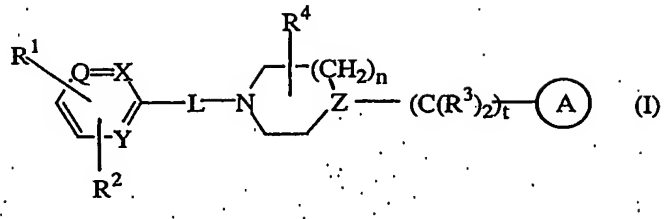
Claims

1. A compound of formula (I),

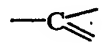


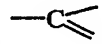
(I)

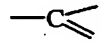
the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

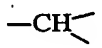
n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

t is 0, 1, 2, 3 or 4 and when t is 0 then a direct bond is intended;

each Q is nitrogen or  ;

each X is nitrogen or  ;

each Y is nitrogen or  ;

each Z is nitrogen or  ;

R^1 is $-C(O)NR^7R^8$, $-NHC(O)R^9$, $-C(O)-C_{1-6}$alkanediylSR^9, $-NR^{10}C(O)N(OH)R^9$, $-NR^{10}C(O)C_{1-6}$alkanediylSR^9, $-NR^{10}C(O)C{=}N(OH)R^9$ or another Zn-chelating-group

wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl or aminoaryl;

R^9 is independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, arylC_{1-6}alkyl, C_{1-6}alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R^{10} is independently selected from hydrogen or C_{1-6}alkyl;

R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, di(C_{1-6}alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;

-L- is a direct bond or a bivalent radical selected from C_{1-6}alkanediyl, C_{1-6}alkanediyloxy, amino, carbonyl or aminocarbonyl;

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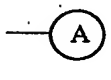
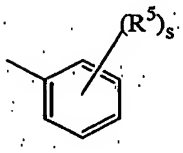
each R^3 independently represents a hydrogen atom and one hydrogen atom can be replaced by a substituent selected from aryl;

R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, hydroxycarbonyl, aminoC_{1-6}alkyl, aminocarbonylC_{1-6}alkyl, hydroxycarbonylC_{1-6}alkyl, hydroxyaminocarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;



is a radical selected from



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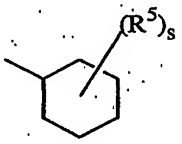

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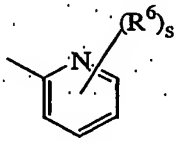

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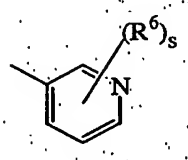

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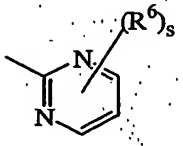

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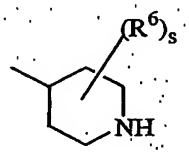

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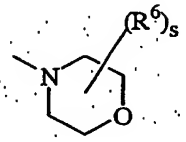

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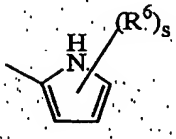

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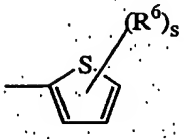

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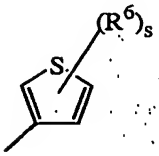

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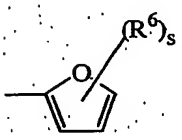

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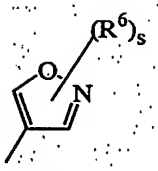

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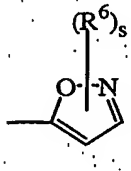

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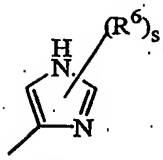

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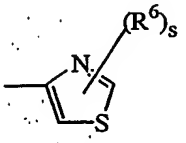

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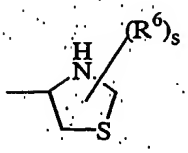

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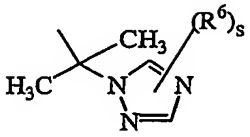
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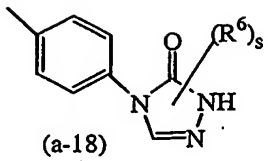
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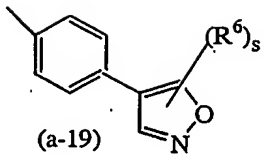
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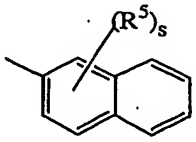
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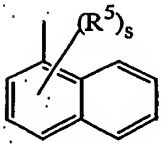
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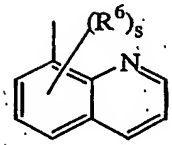
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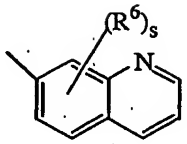
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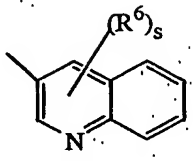
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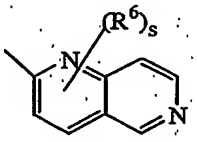
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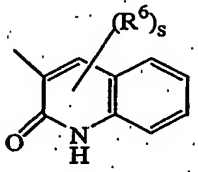
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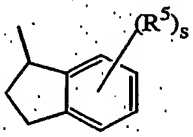
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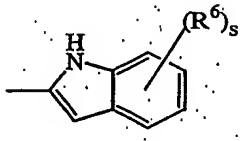
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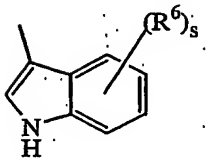
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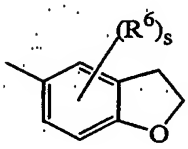
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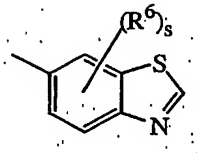
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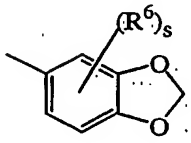
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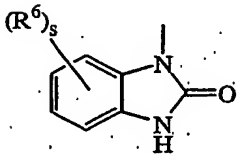
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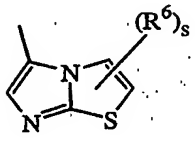
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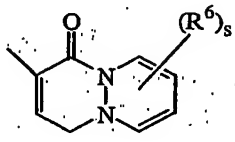
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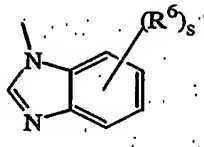
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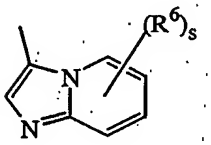
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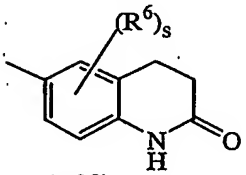
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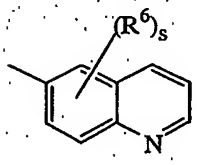
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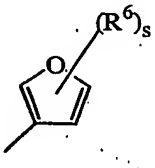
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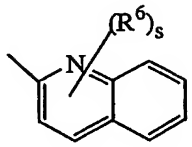
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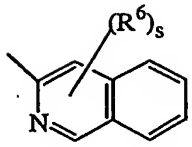
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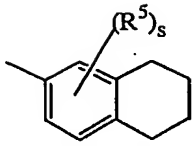
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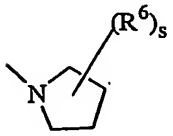
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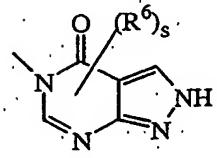
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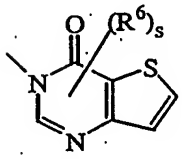
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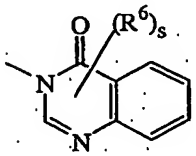
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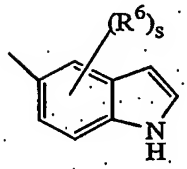
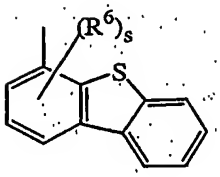
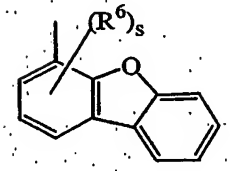
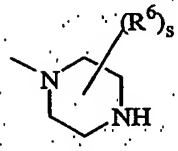

(a-48)


(a-49)


(a-50)


(a-51)

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R^5 and R^6 are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyl substituted with aryl and C_{3-10}cycloalkyl; C_{1-6}alkyloxy; C_{1-6}alkyloxyC_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; cyanoC_{1-6}alkyl; hydroxyC_{1-6}alkyl; hydroxyC_{1-6}alkyloxy; hydroxyC_{1-6}alkylamino; aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminocarbonyl; di(hydroxyC_{1-6}alkyl)amino; (aryl)(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy; di(C_{1-6}alkyl)aminoC_{1-6}alkylamino; di(C_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; arylsulfonyl; arylsulfonylamino; aryloxy; aryloxyC_{1-6}alkyl; arylC_{2-6}alkenediyl; di(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)amino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; aminosulfonylamino(C_{1-6}alkyl)amino; aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)amino; di(C_{1-6}alkyl)aminosulfonylamino(C_{1-6}alkyl)aminoC_{1-6}alkyl; cyano; thiophenyl; thiophenyl substituted with di(C_{1-6}alkyl)aminoC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylpiperazinylC_{1-6}alkyl, hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl,

hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl, di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl, C_{1-6}alkyloxypiperidinyl, C_{1-6}alkyloxypiperidinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, hydroxyC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, or di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; piperidinylC_{1-6}alkyloxy; morpholinyl; C_{1-6}alkylmorpholinyl; morpholinylC_{1-6}alkyloxy; morpholinylC_{1-6}alkyl; morpholinylC_{1-6}alkylamino; morpholinylC_{1-6}alkylaminoC_{1-6}alkyl; piperazinyl; C_{1-6}alkylpiperazinyl; C_{1-6}alkylpiperazinylC_{1-6}alkyloxy; piperazinylC_{1-6}alkyl; naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl; C_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkylpiperazinylC_{1-6}alkylamino; C_{1-6}alkylpiperazinylC_{1-6}alkylaminoC_{1-6}alkyl; C_{1-6}alkylpiperazinylsulfonyl; aminosulfonylpiperazinylC_{1-6}alkyloxy; aminosulfonylpiperazinyl; aminosulfonylpiperazinylC_{1-6}alkyl; di(C_{1-6}alkyl)aminosulfonylpiperazinyl; di(C_{1-6}alkyl)aminosulfonylpiperazinylC_{1-6}alkyl; hydroxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; C_{1-6}alkyloxypiperidinyl; C_{1-6}alkyloxypiperidinylC_{1-6}alkyl; piperidinylaminoC_{1-6}alkylamino; piperidinylaminoC_{1-6}alkylaminoC_{1-6}alkyl; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylamino; (C_{1-6}alkylpiperidinyl)(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkylaminoC_{1-6}alkyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkyloxyC_{1-6}alkylpiperazinylC_{1-6}alkyl; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)amino; (hydroxyC_{1-6}alkyl)(C_{1-6}alkyl)aminoC_{1-6}alkyl; hydroxyC_{1-6}alkylaminoC_{1-6}alkyl; di(hydroxyC_{1-6}alkyl)aminoC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyl; pyrrolidinylC_{1-6}alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl substituted with two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC_{1-6}alkyl; quinolinyl; indole; phenyl; phenyl substituted with one, two or three substituents independently selected from halo, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, hydroxyC_{1-4}alkyl, trifluoromethyl, trifluoromethyloxy, hydroxyC_{1-4}alkyloxy, C_{1-4}alkylsulfonyl, C_{1-4}alkyloxyC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonyl, aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)aminoC_{1-4}alkyloxy, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)aminocarbonyl, di(C_{1-4}alkyl)aminoC_{1-4}alkyl, di(C_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)amino(C_{1-4}alkyl)aminoC_{1-4}alkyl,

di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)amino,
di(C_{1-4}alkyl)aminoC_{1-4}alkyl(C_{1-4}alkyl)aminoC_{1-4}alkyl,
aminosulfonylamino(C_{1-4}alkyl)amino,
aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-4}alkyl,
di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)amino,
di(C_{1-4}alkyl)aminosulfonylamino(C_{1-4}alkyl)aminoC_{1-6}alkyl, cyano,
piperidinylC_{1-4}alkyloxy, pyrrolidinylC_{1-4}alkyloxy, aminosulfonylpiperazinyl,
aminosulfonylpiperazinylC_{1-4}alkyl, di(C_{1-4}alkyl)aminosulfonylpiperazinyl,
di(C_{1-4}alkyl)aminosulfonylpiperazinylC_{1-4}alkyl, hydroxyC_{1-4}alkylpiperazinyl,
hydroxyC_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkyloxypiperidinyl,
C_{1-4}alkyloxypiperidinylC_{1-4}alkyl, hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinyl,
hydroxyC_{1-4}alkyloxyC_{1-4}alkylpiperazinylC_{1-4}alkyl,
(hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)amino, (hydroxyC_{1-4}alkyl)(C_{1-4}alkyl)aminoC_{1-4}alkyl,
di(hydroxyC_{1-4}alkyl)amino, di(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkyl, furanyl, furanyl
substituted with –CH=CH-CH=CH-, pyrrolidinylC_{1-4}alkyl, pyrrolidinylC_{1-4}alkyloxy,
morpholinyl, morpholinylC_{1-4}alkyloxy, morpholinylC_{1-4}alkyl,
morpholinylC_{1-4}alkylamino, morpholinylC_{1-4}alkylaminoC_{1-4}alkyl, piperazinyl,
C_{1-4}alkylpiperazinyl, C_{1-4}alkylpiperazinylC_{1-4}alkyloxy, piperazinylC_{1-4}alkyl,
C_{1-4}alkylpiperazinylC_{1-4}alkyl, C_{1-4}alkylpiperazinylC_{1-4}alkylamino,
C_{1-4}alkylpiperazinylC_{1-4}alkylaminoC_{1-6}alkyl, tetrahydropyrimidinylpiperazinyl,
tetrahydropyrimidinylpiperazinylC_{1-4}alkyl, piperidinylaminoC_{1-4}alkylamino,
piperidinylaminoC_{1-4}alkylaminoC_{1-4}alkyl,
(C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylamino,
(C_{1-4}alkylpiperidinyl)(hydroxyC_{1-4}alkyl)aminoC_{1-4}alkylaminoC_{1-4}alkyl,
pyridinylC_{1-4}alkyloxy,
hydroxyC_{1-4}alkylamino, hydroxyC_{1-4}alkylaminoC_{1-4}alkyl,
di(C_{1-4}alkyl)aminoC_{1-4}alkylamino, aminothiadiazolyl,
aminosulfonylpiperazinylC_{1-4}alkyloxy, or thiophenylC_{1-4}alkylamino;

each R^5 and R^6 can be placed on the nitrogen in replacement of the hydrogen;

aryl in the above is phenyl, or phenyl substituted with one or more substituents each independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl, cyano or hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein n is 1 or 2; t is 0, 1, 2 or 4; each Q is —C<; R^1 is –C(O)NH(OH); R^2 is hydrogen or nitro; -L- is a direct bond or a bivalent radical selected from C_{1-6}alkanediyl; R^4 is hydrogen; —(A) is a radical

selected from (a-1),(a-2), (a-3), (a-5), (a-6), (a-11), (a-18), (a-20), (a-21), (a-32), (a-33), (a-47) or (a-51); each s is independently 0, 1, 2, or 4; each R^5 and R^6 are independently selected from hydrogen; halo; trihaloC_{1-6}alkyl; C_{1-6}alkyl; C_{1-6}alkyl substituted with aryl and C_{3-10}cycloalkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; benzofuranyl; naphtalenylsulfonyl; pyridinyl substituted with aryloxy; phenyl; or phenyl substituted with one substituent independently selected from hydroxyC_{1-4}alkyl or morpholinylC_{1-4}alkyl.

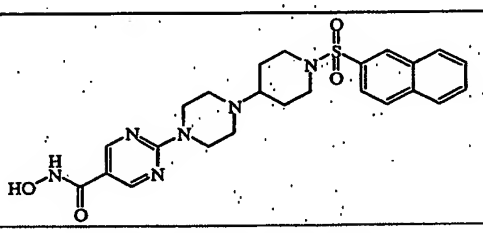
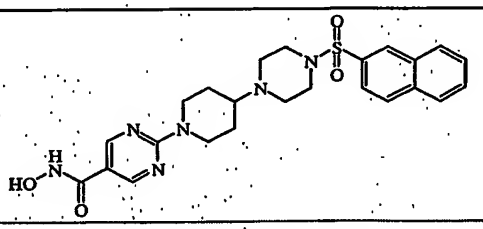
3. A compound as claimed in claim 1 wherein t is 1, 2, 3, or 4;
R^1 is $-C(O)NR^7R^8$, $-C(O)-C_{1-6}$alkanediylSR^9, $-NR^{10}C(O)N(OH)R^9$, $-NR^{10}C(O)C_{1-6}$alkanediylSR^9, $-NR^{10}C(O)C{=}N(OH)R^9$ or another Zn-chelating-group wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy, hydroxyC_{1-6}alkyl or aminoC_{1-6}alkyl;
R^2 is hydrogen, halo, hydroxy, amino, nitro, C_{1-6}alkyl, C_{1-6}alkyloxy, trifluoromethyl or di(C_{1-6}alkyl)amino;
-L- is a direct bond or a bivalent radical selected from C_{1-6}alkanediyl, C_{1-6}alkanediyloxy, amino or carbonyl;
R^4 is hydrogen, hydroxy, amino, hydroxyC_{1-6}alkyl, C_{1-6}alkyl, C_{1-6}alkyloxy, arylC_{1-6}alkyl, aminocarbonyl, aminoC_{1-6}alkyl, C_{1-6}alkylaminoC_{1-6}alkyl or di(C_{1-6}alkyl)aminoC_{1-6}alkyl;
—(A) is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) and (a-51);
each s is independently 0, 1, 2, 3 or 4;
R^5 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC_{1-6}alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C_{1-6}alkyl; C_{1-6}alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C_{1-6}alkylmorpholinyl; piperazinyl; C_{1-6}alkylpiperazinyl; hydroxyC_{1-6}alkylpiperazinyl; C_{1-6}alkyloxypiperidinyl; pyrazoly; pyrazolyl substituted with one or two substituents selected from C_{1-6}alkyl or trihaloC_{1-6}alkyl; pyridinyl; pyridinyl substituted with C_{1-6}alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole;

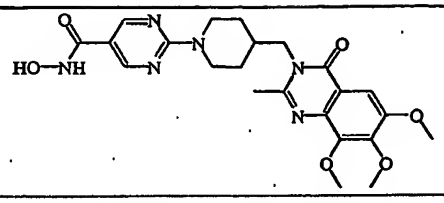
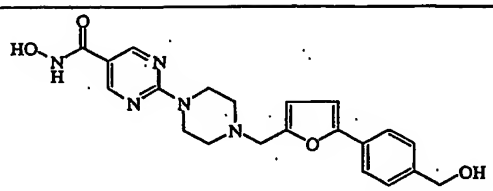
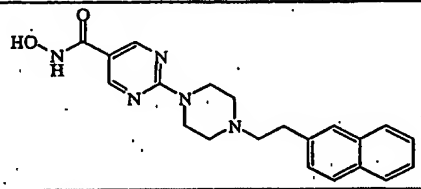
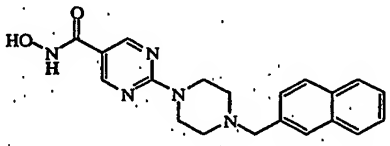
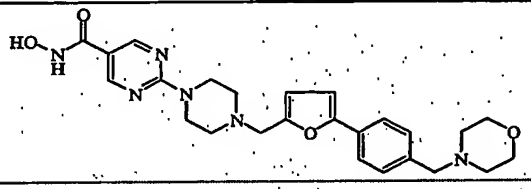
phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl;

R^6 is hydrogen; halo; hydroxy; amino; nitro; trihaloC_{1-6}alkyl; trihaloC_{1-6}alkyloxy; C_{1-6}alkyl; C_{1-6}alkyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkylsulfonyl; hydroxyC_{1-6}alkyl; aryloxy; di(C_{1-6}alkyl)amino; cyano; pyridinyl; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C_{1-6}alkyl, C_{1-6}alkyloxy or trifluoromethyl.

4. A compound as claimed in claim 1 and 2 wherein n is 1; t is 0 or 1; each Q is —C=; each X is nitrogen; each Y is nitrogen; R^1 is –C(O)NH(OH); R^2 is hydrogen; -L- is a direct bond; each R^3 independently represents a hydrogen atom; R^4 is hydrogen; —(A) is a radical selected from (a-6), (a-11), (a-20), (a-47) or (a-51); each s is independently 0, 1, or 4; and each R^5 and R^6 are independently selected from hydrogen; C_{1-6}alkyl; C_{1-6}alkyloxy; naphtalenylsulfonyl; or phenyl substituted with hydroxyC_{1-4}alkyl or morpholinylC_{1-4}alkyl.

5. A compound according to claim 1, 2 and 4 selected from compounds No. 3, No. 4, No. 8, No. 5, No. 7, No. 6 and No. 9.

	
0.91 $C_2HF_3O_2$; Co. No. 3	0.86 $C_2HF_3O_2$; Co. No. 4

	
$C_2HF_3O_2$ (1:1); Co. No.8	0.83 $C_2HF_3O_2$; Co. No.5
	
0.79 $C_2HF_3O_2$; Co. No.7	0.83 $C_2HF_3O_2$; Co. No.6
	
0.47 H_2O .1.99 $C_2HF_3O_2$; Co. No.9	

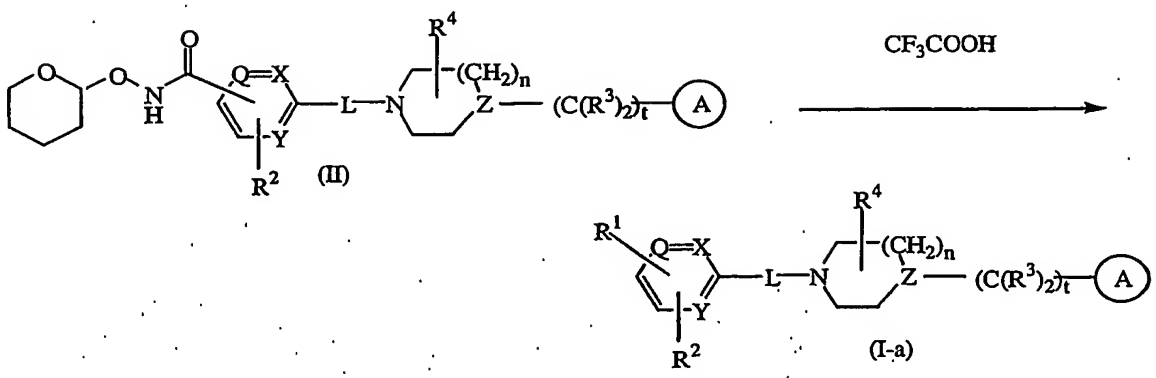
6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 5.

7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.

8. A compound as claimed in any of claims 1 to 5 for use as a medicine.

9. Use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of proliferative diseases.

10. A process for preparing a compound as claimed in claim 1, characterized by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I-a), wherein R^1 is –C(O)NH(OH)



11. A method of detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound as defined in claim (I) and a HDAC.

12. A combination of an anti-cancer agents and a HDAC inhibitor as claimed in any of claims 1 to 5.

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